September 9, 1998

This document was submitted to EPA by a registrant in connection with EPA's evaluation of this chemical and it is presented here exactly as submitted.

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RHÔNE-POULENC 12/OPP # 34144

RHÔNE-POULENC AG COMPANY

August 19, 1998

Ms. Kathryn Boyle
Special Review & Reregistration Division (H7508W)
Office of Pesticide Programs
U. S. Environmental Protection Agency
Room 266A, Crystal Mall 2
1921 Jefferson Davis Highway
Arlington, VA 22202

Dear Ms. Boyle:

RE: Ethoprop/HED RED Chapter and Risk Assessments

This letter serves as a response to your correspondence of July 20, 1998 in which Mr. Jack Housenger asked us to address only the factual errors (mathematical, computational, typographical, etc...) that may have occurred in the preliminary risk assessement. As you well know, we can address this issue but it would be meaningless unless we addressed all aspects of the preliminary risk assessment since they are so closely tied together.

Acute Dietary Risk

As far as the tox end point (0.025 mg/kg/day for acute dietary) used in the preliminary dietary risk assessment is concerned, it is the same as that used by Rhône-Poulenc in the Monte Carlo Analysis/Risk Assessment submitted previously to the Agency.

The HED RED Chapter mentions the Tier I Acute Analysis using the DRES analysis. As you are aware, a Monte Carlo Assessment was submitted on April 22, 1998 (MRID # 44543801). This has been reviewed by the Agency but written comments are not available to us at this time. All crops were included in this assessment in addition to estimated crop treated data for bananas (imported crop). Bananas are a major contributor when 100% crop treated is assumed at tolerance. This is an important issue because only 3% of the imported banana crop is treated with ethoprop and this is a conservative estimate.

Results from the Monte Carlo Analysis showed that using the 99.9th percentile of exposure for the overall US population resulted in a MOE of 270. For Females 13+, the 99.9th percentile of exposure resulted in a MOE of 414. For infants, an acute exposure resulted in a MOE of 114 at the 99.9th percentile. As you can see, all of these exposures

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are acceptable when a MOE of 100 or more is needed for the acute exposure to ethoprop.

Chronic Dietary Risk

The Rfd used in the chronic dietary risk assessments was 0.0001 mg/kg/day. This is also the Rfd Rhône-Poulenc has calculated based on effects seen in the subchronic and chronic dog studies. We also agree with the Agency's determination that the "chronic dietary risk is below the Agency's level of concern for the general U.S. population and for all subgroups."

Metabolite Information Used in the Risk Assessments

Historically, ethoprop field studies measured only the parent and the metabolite, O-ethyl-S-propylphosphorothioate (MIV[1]). Recently, the EPA Metabolism Committee determined that MIV is not of toxicological concern for chronic non-cancer dietary risk or for acute dietary risk. EPA identified two additional metabolites, O-ethyl-O-methyl-S-propylphophorothioate (OME) and O-ethyl-S-methyl-S-propylphosphorodithioate (SME) that are of concern for both chronic (cancer and non-cancer) and acute dietary risk.

To determine the total residue level from field studies, the Agency used metabolism data to make "conservative" assumptions about the ratio of parent to metabolites. The methodology is outlined below.

1. Chronic cancer risk: Ratios were calculated from metabolism studies by dividing total residues of concern (parent plus OME, SME and MIV) by the sum of parent plus MIV. To determine the total toxic residue for use in the chronic cancer dietary risk assessment, the average total residue (parent plus MIV) from field trials was multiplied by the average ratio (2.1) calculated.

2. Chronic non-cancer risk: Ratios were calculated from metabolism studies by dividing total residues of concern (parent plus OME, SME) by the sum of parent plus MIV. To determine the total toxic residue, the average total residue (parent plus MIV) from field trial studies was multiplied by the average ratio (2.8) calculated.

3. Acute dietary risk: Ratios were calculated from metabolism studies by dividing total residues of concern (parent plus OME, SME) by the sum of

[1] EPA designation; registrant identifies this metabolite as M1 in field studies.

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(2)

parent plus MIV. To determine the total toxic residue, the total residue (parent plus MIV) from field trial studies was multiplied by the highest ratio (5.3) calculated.

Calculations of ratios for the chronic non-cancer and acute dietary analyses should not include the MIV metabolite, since the MIV metabolite is not of toxicological concern for these types of risk assessments. Likewise, the MIV metabolite should not be included in the expression of the total toxic residue from field studies. Including MIV overestimates potential ethoprop residues in foods.

Regardless of the methodology used to calculate the ratios, only those metabolism studies in which parent and all metabolites of concern were present at levels above the sensitivity of the analytical method should be used for the calculation. Excluding residues of metabolites that are reported as non detects results in a ratio that may not accurately reflect the relationship between parent and metabolites. It should be noted that the highest ratio (and used to estimate total residues for use in the acute dietary assessment) was calculated from a study in which neither OME nor MIV were detected.

In addition, the Agency did not address the situation where no detectable residues of either parent or metabolites were observed in the metabolism studies. Results of these studies suggest that no metabolites will be present if parent residues are not observed.

The majority of the samples analyzed in ethoprop field studies did not contain measurable residues of either parent or MIV—even at exaggerated application rates. The Agency assumed a value of half the limit of detection for both parent and MIV, then summed these values prior to multiplying by the calculated ratio. To multiply a limit of detection value by the calculated ratio of parent to metabolites grossly overestimates residue levels in foods. A more realistic estimate would be to simply assume half the limit of detection value of the parent—with no further adjustments.

Oncogenic Risk

EPA Classification of Ethoprop

In correspondence dated 2 October 1997, the United States EPA issued a report of the Cancer Assessment Review Committee regarding the carcinogenic potential of ethoprop. We would like to reiterate our position that ethoprop is not a carcinogen and that the 1992 rat chronic/oncogenicity study provides no evidence of an oncogenic potential for ethoprop. Accordingly, we disagree with the EPA positioning this compound as "likely" human carcinogen to be regulated by linear low dose extrapolation.

In a March 5, 1998 meeting, Rhône-Poulenc presented data showing that survival was markedly increased in both male and female high dose rats in the 1992 study, i.e., the high dose animals were healthier than control animals. The two year survival rate in male rats was twice that of controls (58% vs 29%, $p<0.001$), and for females was 1.5 that of controls (62% vs 41%, $p=0.012$). The tumors discussed by the committee were all common, age related, proliferative lesions. Since cancer is an old age disease, it is normal for older animals to have increased raw incidences of normal age related tumors.

Also, the statistical approach taken in the EPA review is not considered to be optimal. The Peto Prevalence Test is an older method for accounting for survival differences in the analysis of non-lethal tumor data that has the limitation of being sensitive to the time period intervals selected for the analysis. A statistical method currently considered to be superior is the logistic regression approach used by the National Toxicology program which does not have this limitation. Appropriate statistics designed to take into account age related differences between treatment groups were not significant for any of the tumor types examined.

In summary, the carcinogenicity studies on ethoprop demonstrate that it should not be considered to be oncogenic in any tissue system. For each of the tissues highlighted by the EPA reviewers, there are compelling reasons to dismiss the "indications" of carcinogenicity in addition to the fact that none of the findings are statistically significant. The study pathologist concluded there was no evidence of oncogenicity in the 1992 rat study. Further, California EPA performed its own independent analysis of the data and concluded there was no evidence of an oncogenic potential of ethoprop. Thus the classification of likely human carcinogen by the US EPA is unwarranted. Ethoprop should be classified as noncarcinogenic and the reference dose should remain at 0.0001 mg/kg/day as established by the RfD Peer Review Committee on April 24, 1997.

Occupational and Residential (Non-Cancer) Risk

We agree with the Agency that a home use risk assessment is not needed since there are no homeowner uses of this product.

Occupational Cancer Risk

We also agree with the Agency that a chronic occupational exposure assessment was not performed since no chronic exposure scenarios exist.

Please be aware that two of the four exposure scenarios (listed below) that have a carcinogenic risk of 10^{-3} or greater which exceeds the Agency's level of concern will be deleted from the ethoprop labels. The other two scenarios are being further evaluated at this time.

- Mixing/loading liquid formulations for chemigation
- Mixing/loading/applying liquid formulations with low-pressure hand-wand sprayer

Rhône-Poulenc intends to meet with EPA exposure specialists soon to further refine the occupational exposure risk assessments. For example, Rhône-Poulenc does not agree with the EPA calculation for combined dermal and inhalation exposure wherein the dermal exposure was converted to oral-equivalents assuming 100% absorption. Comparison of the oral and dermal NOELs provide convincing evidence that the dermal absorption for ethoprop is not 100% and accepted methods exist to modify the dermal exposure value, when both dermal and oral NOELs are available, to provide more realistic dermal exposure in oral equivalents.

Data Requirements

Product and Residue Chemistry Chapter

Residue Chemistry

We will amend the labels to make them consistent with the current residue trials submitted to the Agency.

Field Rotational Crop Study: The field rotational crop study (MRID # 44350201) was submitted August 13, 1997. In EPA's March 9, 1998 review of the study, they felt plant back restrictions of 30 days for leafy vegetable crops and 8 months for small grains was needed as well as additional residue trials on radish. On April 18, 1998, Rhône-Poulenc informed the Agency that we would not be performing additional residue trials and that we agreed to modify our label to reflect that decision. Also in that letter we stated we would agree to the 30 day plant back restriction for leafy vegetables but that the data in the field rotational crop study indicated that a 4 month (as opposed to an 8 month) plant back restriction for small grains was appropriate. As of this date, we've not received any information on their consideration of our proposal.

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Metabolite Residue Studies: The use of metabolite data in the dietary exposure assessments is addressed above under "Metabolite Information Used in the Risk Assessments."

Product Chemistry

Rhône-Poulenc recognizes the need for a UV/Visibility absorbance since it is now a guideline requirement for technical grade active ingredients (OPPTS guidelines, August, 1996). This guideline has not been submitted in the past since both the formulation and residue enforcement methods are based on GC procedures, as is typical for chemicals in this class of compound, alkyl organophosphates. Data will be submitted to comply with this guideline at a later date.

Toxicology

Preparation for the cholinesterase study for the M1 metabolite is in progress.

Occupational Exposure Assessment

It is recommended that aerial use, greenhouse use, and sod farm use scenarios be further assessed. Again, as mentioned above, Rhône-Poulenc intends to meet with EPA exposure specialists soon to further refine the occupational exposure risk assessments on these scenarios and the other use pattern scenarios. There are concerns with the way EPA conducted their occupational risk assessments that are discussed above.

These are some of the areas of concern with the HED RED Chapter and risk assessments we feel need to be addressed. Of course some of the issues in this correspondence will be taken further through additional position papers and meetings with the EPA.

Please contact me at 919/549-2787 if you have any questions.

Sincerely,

Lizbeth R. Simila

Lizbeth R. Simila
Registration Manager

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